PTO 05-3023 translation by USPTO of JP 04-145067 A2

CY=JA DATE=19920519 KIND=A
PN=04-145067

Examiner Note
rec'd 4/20/05

# HETEROACETIC AMIDE DERIVATIVE AND GERMICIDE FOR AGRICULTURE AND HORTICULTURE

[Hetero sakusan amido yudotai oyobi noengeiyo sakkinzai]

Hiromichi Ishikawa, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. April 2005

Translated by: FLS, Inc.

| | | |
|---|---|---|
| PUBLICATION COUNTRY | (19): | JP |
| DOCUMENT KIND | (12): | A |
| | (13): | PUBLISHED UNEXAMINED PATENT APPLICATION (Kokai) |
| PUBLICATION DATE | (43): | 19920519 [WITHOUT GRANT] |
| PUBLICATION DATE | (45): | 19920519 [WITH GRANT] |
| APPLICATION NUMBER | (21): | 02-265231 |
| APPLICATION DATE | (22): | 19901004 |
| PRIORITY DATE | (32): | |
| ADDITION TO | (61): | |
| INTERNATIONAL CLASSIFICATION | (51): | A01N 43/40; A01N 43/46; A01N 43/50; A01N 43/56; A01N 43/653; C07D 231/12; C07D 233/60; C07D249/08; C07D 295/04 |
| DOMESTIC CLASSIFICATION | (52): | |
| PRIORITY COUNTRY | (33): | |
| PRIORITY NUMBER | (31): | |
| PRIORITY DATE | (32): | |
| INVENTOR | (72): | ISHIKAWA, HIROMICHI; TANIGUCHI, MASAKAZU; KAJIKAWA, KAZUO. |
| APPLICANT | (71): | Hokko Kagaku Ltd. |
| TITLE | (54): | Heteroacetic amide derivative and germicide for agriculture and horticulture |
| FOREIGN TITLE | [54A]: | Hetero sakusan amido yudotai oyobi noengeiyo sakkinzai |

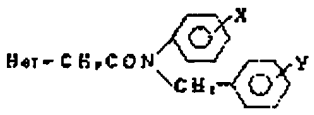
Specification /285*

1. Name of this invention

HETEROACETIC AMIDE DERIVATIVE AND GERMICIDE FOR AGRICULTURE AND HORTICULTURE

2. Claim(s)

[Claim 1] Heteroacetic amide derivative expresses in the following formula:



(where X and Y denote same or different atom, halogen or lower alkyl; Het denotes piperidino, methylpiperidino, dimethylpiperidino, hexamethyleneimino, pyrazolyl, imidazolyl or triazolyl).

[Claim 2] Germicide for agriculture and horticulture containing the heteroacetic amide derivative according to Claim 1 as a valid substance.

3. Detailed Explanation of this Invention

1) [Technological Field]

This invention pertains to a new heteroacetic amide derivative and is particularly associated with N-phenyl, N-benzyl hetero acetic amide derivative expressed by formula (I) described later in this article, and germicide for agriculture and horticulture containing said derivative as a valid substance. Therefore, this invention is

* Numbers in the margin indicate pagination in the foreign text.

useful to the chemical industry, agriculture and horticulture field, where this invention is particularly valuable in the farming product production field.

2) [Conventional Technology]

N-phenyl and N-(p-chloro benzyl) pyrrolidine-il acetic acid amide, which share a similar chemical structure, are known to provide a local anesthetic function [Chemical Abstract, Vol. 79, 126414 n (1973)]. However, there has been no report on N-phenyl and N-benzyl hetero acetic amide derivative expressed by formula (I) of this invention (described later). Also, germicide effect of these materials for agriculture and horticulture has not been reported.

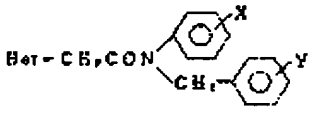
3) [Problems to be Solved by this Invention] /476

Conventionally known N-phenyl and N-(p-chloro benzyl) pyrrorolidine-il acetic acid hardly function as a germicide for agriculture and horticulture. On the other hand, various chemicals are used to prevent agricultural diseases [Betobyo (downy mildew-Peronospora farinose), Ekibyo (late blight), Udonko-byo (powdery mildew), rust, etc.] which are serious diseases to fruits, vegetables, and grains. However, these chemicals eventually become unusable due to chemical resistance or their uses will be restricted. Therefore, germicide of a new medical skeletal structure different from those of conventional chemicals is needed by the industries. The object of present invention is to provide a new germicide meeting this need.

[Constituents of this invention]]

1) Means to solve the problems

The developers of this invention synthesized numerous compounds in order to achieve the above-mentioned object and examined the usefulness of these compounds. As a result, heteroacetic amide derivative expressed in the following formula:



(where X and Y denote same or different atoms, halogens or lower alkyls; Het denotes piperidino, methylpiperidino, dimethylpiperidino, hexamethyleneimino, pyrazolyl, imidazolyl or triazolyl).

Said lower alkyl may be straight chain type or branched chain type. In addition, the "lower" alkyl denotes alkyl having 1 - 6 carbons.

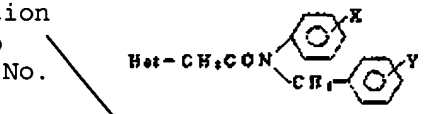
The second aspect of this invention is a germicide for agriculture and horticulture containing a heteroacetic amide derivative expressed by formula (I) described above as a valid substance.

Practical examples of compounds of this invention expressed by formula (I) are described in Table 1.

Note that these compound No. are referenced by the operational examples and experiment examples explained below.

Table 1

Substitution group Compound No.

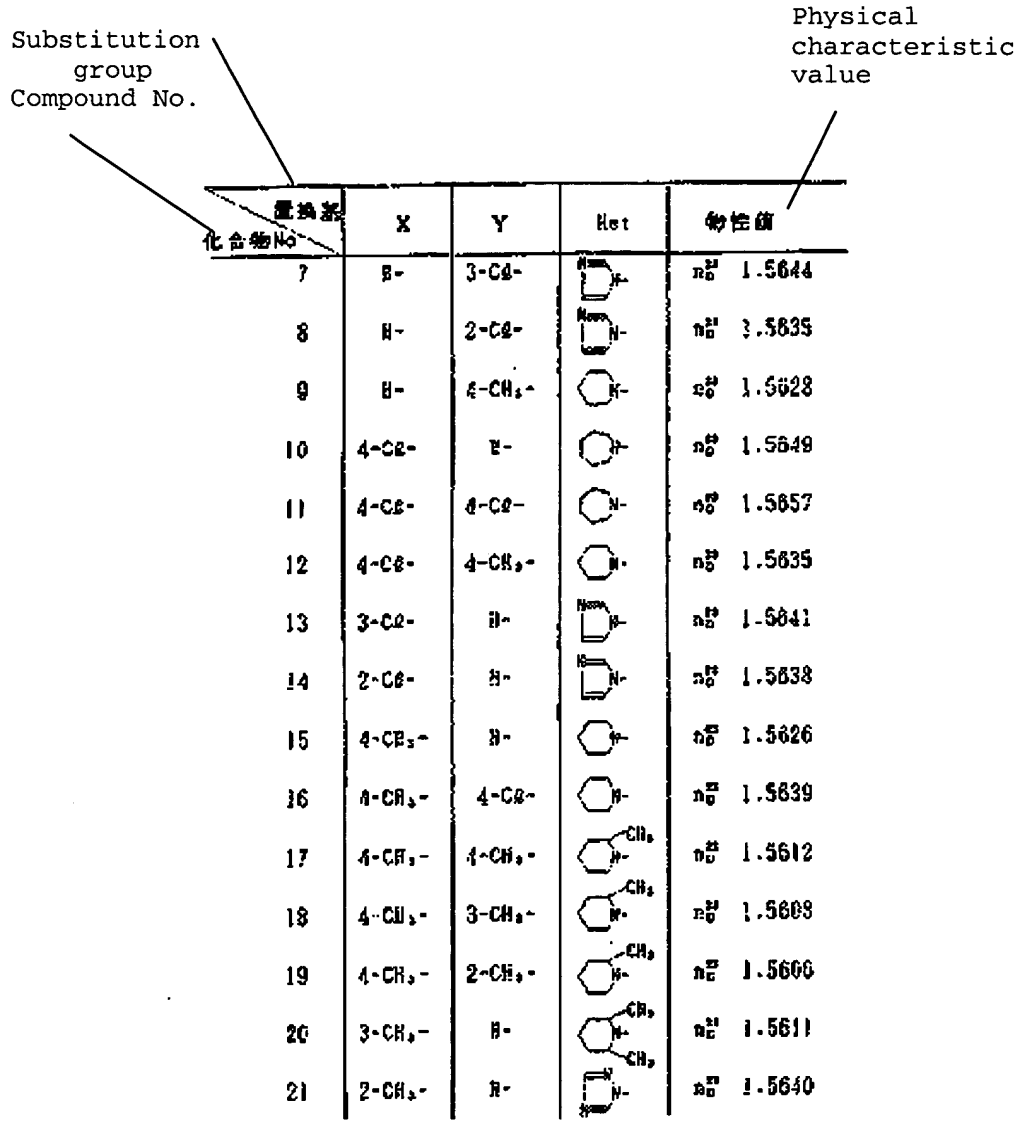


(I)

Physical characteristic value

| 置換基 / 化合物No | X | Y | Het | 物性値 |
|---|---|---|---|---|
| 1 | H- | H- |  | $n_D^{25}$ 1.5633 |
| 2 | H- | H- |  | $n_D^{25}$ 1.5641 |
| 3 | H- | H- |  | $n_D^{25}$ 1.5649 |
| 4 | H- | 4-Cl- |  | m.p. 49-50℃ |
| 5 | H- | 4-Cl- |  | $n_D^{25}$ 1.5651 |
| 6 | H- | 4-Cl- |  | m.p. 102-103℃ |

Table 1 (continued)



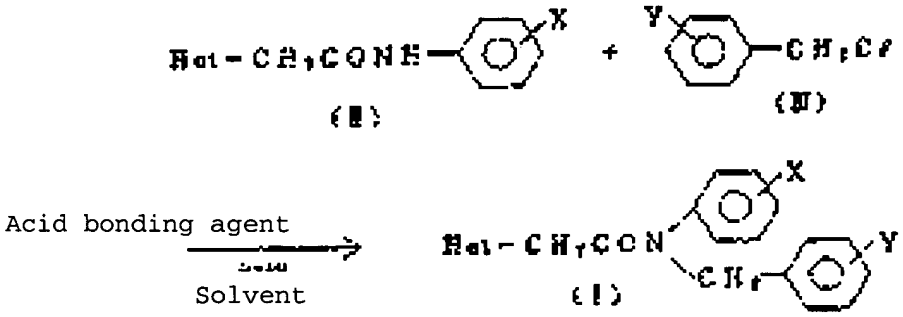

2) Operation /477

Compounds expressed by formula (I) of this invention are new compounds functioning as active ingredients of germicide for agriculture and horticulture.

3) Operational example (Part 1)

Production method of compounds of this invention:

Compounds expressed by formula (I) can be produced by the following method. That is, the compound can be produced by reacting a N-phenyl heteroacetic acid amide derivative expressed by formula (II) and benzyl chloride derivative expressed by formula (III) in a solvent in the presence of acid bonding agent:




(where X, Y, and Het denote the same materials as described above.)

Examples of acid bonding agent used in this reduction reaction are inorganic salts, such as hydrogenated sodium, sodium amide, potassium carbide, and the like, and organic salts, such as triethyl amine, pyridine, and the like.

Examples of solvent are hydrocarbons, such as toluene, hexane, etc., halogenated hydrocarbon, such as chloroform, chloro benzene, etc., ethers, such as dioxane, tetrahydrofuran, etc., nitrile materials, such as acetonitrile, propionitrile, etc.

Although reaction can progress at room temperature, by heating to a boiling point range of the solvent, the reaction duration can be

shortened. After the reaction, water and an organic solvent (e.g., benzene, toluene, tetrahydrofuran, chloroform, etc.) are added to separate the object material, and the solvent is removed. Subsequently, the compound of this invention can be obtained.

Operational examples 1 - 2 describes the production examples based on the above-mentioned technique.

Note that compounds expressed by formula (II) and formula (III), which are raw origination materials, are all conventional materials.

Operational example 1:
Production of N-phenyl, N-(p-chlorobenzyl) pyperridine-1-il acetic acid amide (compound No. 4)

21.8 g of N-(p-chlorobenzyl) pyperridine-1-il acetic acid amide, 16.1 g of p-chlorobenzyl chloride, and 200 ml of chloroform were put in a flask having four inlets (500 ml capacity), in which 10.6 g of triethyl amine were dripped. After the completion of dripping, the mixture was stirred at 60°C for 1 hour. After the mixture was cooled and twice washed with water, the organic layer was dried with anhydrous sodium sulfuric acid, and the solvent was removed through reduced-pressure distillation. As a result, 34.3 g of said compound were obtained as brown crystals. When this compound was recrystallized with an acetic acid ethyl-hexane mixture solvent, the material became light-brownish crystals having a melting point of 49 - 50°C.

Operational example 2:
Production of N-phenyl, N-(p-chlorobenzyl) imidazole-1-il acetic acid amide (compound No. 5)

20.1 g of N-phenyl imidazole acetic acid amide, 16.1 g of p-chlorobenzyl chloride, and 200 ml of chloroform were put in a flask having four inlets (500 ml capacity), to which 17.9 g of potassium carbonate were added and stirred at 80°C for 2 hours. After the mixture was cooled, 300 ml of chloroform was added and twice washed with water. Then, the organic layer was processed in the same manner as described in the operational example 1. As a result, 32.5 g of said compound were obtained as a brownish oily material. When this compound was refined by silica gel column chromatography, the material became a light-brownish oily substance showing $n_o^{23}$ 1.5651.

4) Operational example (part 2):

Production method of germicide for agriculture and horticulture

The germicide for agriculture and horticulture according to the second claim of this invention can be produced by processing the compounds expressed by formula (I) described above with the common prescription method. That is, the compound expressed by formula (I), appropriate carrier, and helper (e.g., surfactant, binder, stabilizer, etc.) are composed to produce a chemical in the form of wettable powder, emulsion, liquid agent, sol agent (floable agent), oil agent, powder, DL (driftless agent) powder, fine powder, row powder, etc. The ratio of substance content in the prepared material is 1 - 90% /478

(weight %; hereafter denotes the same) if the material is in the form of wettable agent, emulsion, sol, or oil. If the material is in the form of powder, DL powder, fine or row powder, the ratio is 0.5 - 5%. In the case of powder, the amount may be 1 - 10%.

To use the germicide for agriculture and horticulture, the following method is usually applied:

When the material is in the form of wettable powder, emulsion, liquid agent, sol agent (floable agent), or oil agent, water is added to dilute the material to 500 - 2,000 times so as to prepare a mixture containing a valid substance at 1 - 10,000 ppm of concentration. Then, 50 - 500 liters, preferably 100 - 300 liters of this diluted solution is sprayed over 10 acres of land.

Moreover, when it is in the form of liquid agent, emulsion, or sol agent (floable agent), the material may be used as a undiluted concentrated solution, or it may be diluted up to 10 times to prepare a fine shrinkable agent (LV sprinkling agent, DLV sprinkling agent, etc.), and sprinkled from the air (50 - 2000 ml per 10 acres) using a helicopter or the like.

Also, when it is in the form of powder, DL powder, or fine or row particles, the material is applied to the infected area (e.g., stem/leaves, soil or water surface, or in the soil) for an amount of 2 - 5 Kg per 10 acres (approx. 50 - 500 g of active substance content).

To produce said germicide for agriculture and horticulture by incorporating the compound expressed by formula (I), the operational examples 3 - 6 described below may be used:

Operational example 3: Powder agent

2 parts of compound No. 17, 1 part of PAP (physical characteristic improvement agent), and 97 parts of clay were uniformly mixed and pulverized to prepare a powder agent containing 2% of active substance.

Operational example 4: Wettable agent

20 parts of compound No. 5, 3 parts of alkyl benzene sulfonic acid potassium, 5 parts of polyoxyethylene nonyl phenyl ether, and 72 parts of white clay were uniformly mixed and pulverized to prepare a wettable agent containing 20% of active substance.

Operational example 5: Emulsion agent

30 parts of compound No. 11, 40 parts of methyl ethyl ketone, and 40 parts of polyoxy ethylene nonyl phenyl ether were mixed and dissolved to prepare an emulsion agent containing 30% of active substance.

Operational example 6: Sol agent

40 parts of compound No. 4, 2 parts of rauryl sulphate, 2 parts of alkyl naphthalene sulfonic acid soda, 1 part of acetoxy propyl cellulose and 55 parts of water were uniformly mixed to prepare a sol agent containing 40% of active substance.

[Effectiveness of this invention]

The new compounds of this invention provides highly useful germicide effect to the serious diseases affecting fruits, vegetables, and wheat [e.g., Betobyo (Peronospora farinose), Ekibyo (infectious disease), Udonko-byo (fungus disease), and rust disease], and therefore, are effective for producing germicide for agriculture and horticulture.

The usefulness and practical examples of compounds expressed by formula (I) of this invention are explained in the experiment examples 1 - 4 described below.

Experiment example 1: Germicide for cucumber Betobyo (Peronospora farinose)

The wettable agent prepared according to the method described in the operational example 1 was diluted to a specific concentration and sprinkled to the second-leave period cucumber seedling (kind: Somo-hanpaku) cultivated in the soil in a pot (9 cm in diameter) in a greenhouse. Then, Pseudoperonospora cubenis pores were rubbed off from infected leaves with a wetted brush and suspended in an aqueous solution (50 ppm) of polyoxyethylene alkyl ether solvent. Then, the pore concentration was adjusted to $5 \times 10^6$ pore count (pieces/ml) and sprayed over the leaves a day after the germicide was sprayed. Then, the tester was left untouched in a greenhouse (20°C, humidity = 100%) for two days to onset the disease. After 6 days from the inoculation, the ratio (%) of disease-infected spotted areas per

leave was examined, and the average infection of leaves were calculated. Then, the germicidal value (%) was computed by the formula described below so as to rate the material based on the standard described below.

This test was performed twice continuously per germicide-applied area.

Moreover, the damages of cucumber caused by the infectious disease were examined based on the following standard. The results are shown in Table 2.

Note that the same evaluation value of germicidal effect and germicide examination index were used in the experiment examples 2 - 4. /479

$$\text{Germicidal value (\%)} = 1 - \frac{\text{Rate (\%) of infected areas in sprayed area}}{\text{Rate (\%) of infected areas in non-sprayed area}} \times 100$$

| Germicidal-effect evaluation value | Value of prevention |
|---|---|
| 5 | 100% |
| 4 | 80 - less than 100% |
| 3 | 60 - less than 80% |
| 2 | 40 - less than 60% |
| 1 | 20 - less than 40% |
| 0 | Less than 20% |

Index for examining damages caused by the disease

5: Extremely high
4: High
3: Notable
2: Small amount
1: Fairly small
0: None

Table 2

(a) (b) (c) (d)

第 2 表

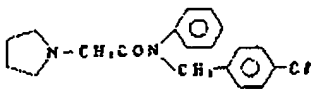
| 供試化合物 No | 散布薬剤濃度 (ppm) | 効果の評価値 | 薬害 |
|---|---|---|---|
| 1 | 100 | 5 | 0 |
| 2 | 100 | 4 | 0 |
| 3 | 100 | 5 | 0 |
| 4 | 100 | 5 | 0 |
| 5 | 100 | 5 | 0 |
| 6 | 100 | 5 | 0 |
| 7 | 100 | 5 | 0 |
| 8 | 100 | 5 | 0 |
| 9 | 100 | 5 | 0 |
| 10 | 100 | 4 | 0 |
| 11 | 100 | 5 | 0 |
| 12 | 100 | 5 | 0 |
| 13 | 100 | 5 | 0 |
| 14 | 100 | 4 | 0 |
| 15 | 100 | 4 | 0 |
| 16 | 100 | 5 | 0 |
| 17 | 100 | 5 | 0 |
| 18 | 100 | 5 | 0 |
| 19 | 100 | 4 | 0 |
| 20 | 100 | 4 | 0 |
| 21 | 100 | 5 | 0 |

Key: a...Test compound; b...Sprinkled germicide concentration; c...Evaluated effect value; d...Damages caused by disease

| Tested compound No. | Sprinkled germicide concentration (ppm) | Evaluated effect value | Damages caused by disease |
|---|---|---|---|
| Comparison chemical A | 100 | 2 | 0 |
| Comparison chemical B | 100 | 2 | 1 |
| Non-sprinkled section | - | 0 (92.6) | - |

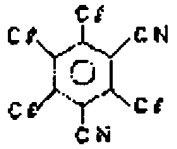
Note) Value in () of non sprinkled section indicates an average rate of infected area per leave.

Comparison chemical A:



[Chemical Abstract, vol 79, 126414n (1973)]

Comparison chemical B:



(General name: Chlorotalonyl)

Experiment example 2: Germicide for tomato disease

The wettable agent prepared according to the method described in the operational example 4 was diluted to a specific concentration. Then, using an automatic spray device, the prepared solution (30 ml per 3 pots) was sprayed over tomatoes in the fifth period seedling (kind: Toko K) cultivated in the soil in vinyl pots (diameter = 9 cm) in a greenhouse. Zoosporangium of infectious tomato disease (Phytophthorainfestans) cultured on one side of pre-sliced potato at 20°C for 3 days were washed off and collected (adjusted to $10^5$ pieces/ml of concentration) and sprayed over tomato leaves using a spray gun. After the pots were stored for 5 days in the greenhouse (20°C, 100% of humidity), the rate (%) of areas infected by the tomato infectious disease was examined on the first - fourth growth-period of the leaves and the average infection area ratio was obtained and compared with the non-treated area in order to generate

a germicidal value (%) and converted to the evaluation value of germicidal effect.

This test was performed as two continuous operations per 1 chemical concentration section.

Moreover, the damages on the tomato leaves caused by the disease were rated using the same standard as those of the experiment example 1. The results are shown in Table 3.

Table 3 /480

第 3 表

| 供試化合物 No | 散布薬液濃度 (ppm) | 効果の評価値 | 薬害 |
|---|---|---|---|
| 1 | 100 | 5 | 0 |
| 2 | 100 | 4 | 0 |
| 3 | 100 | 5 | 0 |
| 4 | 100 | 5 | 0 |
| 5 | 100 | 5 | 0 |
| 6 | 100 | 5 | 0 |
| 7 | 100 | 5 | 0 |
| 8 | 100 | 5 | 0 |
| 9 | 100 | 5 | 0 |
| 10 | 100 | 4 | 0 |
| 11 | 100 | 4 | 0 |
| 12 | 100 | 5 | 0 |
| 13 | 100 | 4 | 0 |
| 14 | 100 | 4 | 0 |
| 15 | 100 | 4 | 0 |
| 16 | 100 | 5 | 0 |
| 17 | 100 | 4 | 0 |
| 18 | 100 | 5 | 0 |
| 19 | 100 | 4 | 0 |
| 20 | 100 | 4 | 0 |
| 21 | 100 | 4 | 0 |

Key: a...Test compound; b...Sprinkled germicide concentration; c...Evaluated effect value; d...Damages caused by disease

| Tested compound No. | Sprinkled germicide concentration (ppm) | Evaluated effect value | Damages caused by disease |
|---|---|---|---|
| Comparison chemical A | 100 | 2 | 1 |
| Comparison chemical B | 100 | 4 | 1 |
| Non-sprinkled section | - | 0 (90.8) | - |

Note 1) Comparison chemicals A and B are the same compounds described in the Table 2.
Note 2) Value in () of non sprinkled section indicates an average rate of infected area per leave.

Experiment example 3: Barley fungus (Udonkobyo) disease

The wettable agent prepared according to the method described in the operational example 4 was diluted to a specific concentration and sprayed over barley at a ratio of 10 ml per 3 pots in the first period seedling (kind: Azumagolden) cultivated in the soil in clay pots (diameter = 9 cm) in a greenhouse. After the pots were left untouched for overnight, the suspension liquid of pores of barley Erysiphe graminis was sprayed for inoculation. Then, 7 days after the inoculation, the rate (%) of areas infected by the Erysiphe graminis of barley disease was examined and the average infection area ratio was obtained and compared with the non-treated area to generate the germicidal value (%) and converted to the evaluation value of germicidal effect.

This test was performed as two continuous operations per 1 chemical concentration section.

Moreover, the damages on the barley caused by the disease were investigated using the same standard as those of the experiment example 1. The results are shown in Table 3.

Table 4

(a) (b) (c) (d)

第 4 表

| 供試化合物 No | 散布薬液濃度 (ppm) | 効果の評価値 | 薬害 |
|---|---|---|---|
| 1 | 250 | 5 | 0 |
| 2 | 250 | 4 | 0 |
| 3 | 250 | 5 | 0 |
| 4 | 250 | 5 | 0 |
| 5 | 250 | 5 | 0 |
| 6 | 250 | 4 | 0 |
| 7 | 250 | 5 | 0 |
| 8 | 250 | 5 | 0 |
| 9 | 250 | 4 | 0 |
| 10 | 250 | 4 | 0 |
| 11 | 250 | 4 | 0 |
| 12 | 250 | 5 | 0 |
| 13 | 250 | 4 | 0 |

Table 4 (continued)

(a) (b) (c) (d)

| 供試化合物 No | 散布薬液濃度 (ppm) | 効果の評価値 | 薬害 |
|---|---|---|---|
| 14 | 250 | 4 | 0 |
| 15 | 250 | 5 | 0 |
| 16 | 250 | 5 | 0 |
| 17 | 250 | 4 | 0 |
| 18 | 250 | 4 | 0 |
| 19 | 250 | 4 | 0 |
| 20 | 250 | 5 | 0 |
| 21 | 250 | 5 | 0 |
| (e) 比較薬剤 A | 250 | 2 | 0 |
| (f) 無散布区 | - | 0(51.3) | - |

Table 4
Key: a…Test compound; b…Sprinkled germicide concentration; c…Evaluated effect value; d…Damages caused by disease; e…Comparison chemical A; f…Non-treated section

Note 1) Comparison chemical A is the same compound described in the Table 2.
Note 2) Value in () of non sprinkled section indicates the number of infection areas on the leaves.

Experiment example 4: Wheat fungus (Udonkobyo) disease

The wettable agent prepared according to the method described in the operational example 4 was diluted to a specific concentration, and this solution (20 ml per 3 pots) was sprayed over wheat in the initial seedling period (kind: Norin No. 61) cultivated in the /481 soil in clay pots (diameter = 9 cm) in a greenhouse. One day later, spores of wheat disease (Puccinia recondite) prepared beforehand were suspended in the sterilization water containing 50 ppm of Tween-20 (polyhoxyethylene sorbitane monoraulate; product of Kao) at a ratio allowing one observation field of the microscope (150 times of magnification) to contain approx. 50 pieces of pores. This pore suspension liquid was sprayed to the wheat leaves for inoculation. After being kept overnight in a greenhouse (20°C; 100% humidity), the leaves were transferred to another greenhouse (20°C) for accelerate the onset of disease. 10 days later, the estimated number of pores was investigated and average count was obtained for acquiring the germicidal value (%) and converted to the evaluation value denoting the germicidal effect.

This test was conducted using three pots per chemical liquid density section.

Moreover, the damages of wheat caused by the disease were examined based on the following standard. The results are shown in Table 5.

$$\text{Germicidal value (\%)} = \left(1 - \frac{\text{Average pore count in the treated section}}{\text{Average pore count in non-treated area}}\right) \times 100$$

Table 5

(a) (b) (c) (d)

第 5 表

| 供試化合物 No | 散布薬剤濃度 (ppm) | 効果の評価値 | 薬害 |
|---|---|---|---|
| 1 | 250 | 4 | 0 |
| 2 | 250 | 4 | 0 |
| 3 | 250 | 5 | 0 |
| 4 | 250 | 5 | 0 |
| 5 | 250 | 5 | 0 |
| 6 | 250 | 5 | 0 |
| 7 | 250 | 5 | 0 |
| 8 | 250 | 5 | 0 |
| 9 | 250 | 4 | 0 |
| 10 | 250 | 4 | 0 |
| 11 | 250 | 4 | 0 |
| 12 | 250 | 4 | 0 |
| 13 | 250 | 4 | 0 |
| 14 | 250 | 5 | 0 |
| 15 | 250 | 4 | 0 |
| 16 | 250 | 4 | 0 |
| 17 | 250 | 4 | 0 |
| 18 | 250 | 5 | 0 |
| 19 | 250 | 4 | 0 |
| 20 | 250 | 4 | 0 |
| 21 | 250 | 5 | 0 |

Key: a...Test compound; b...Sprinkled germicide concentration; c...Evaluated effect value; d...Damages caused by disease

| Tested compound No. | Sprinkled germicide concentration (ppm) | Evaluated effect value | Damages caused by disease |
|---|---|---|---|
| Comparison chemical A | 250 | 2 | 0 |
| Non-sprinkled section | - | 0 (50.8) | - |

Note 1) Comparison chemicals A is the same compound described in the Table 2.

Note 2) Values in () of non sprinkled section indicates average rate of infected area per leave.